## Remarks/Arguments

The foregoing amendment does not add new matter to the specification. Specific support is provided as shown in the following table.

| Claims | Language | Support |
|---|---|---|
| 40 and 66 | less than 2000 daltons in size | Page 16, line 26 |
| 40 and 66 | comprises less than about 20 carbon atoms | Page 14, line 12 |
| 40 and 66 | in aqueous solution | Page 17, lines 21-23 |
| 40 and 66 | has an affinity for interacting with a particular site on the target protein | Page 3, lines 27-28; and page 15, line 15 – page 16, line 23 |
| 64 | the first reactive functionality is an –SH group, masked -SH group, or activated -SH group | Page 6, lines 20-21; page 13, lines 21-22 |
| 65 | said -SH group, masked -SH group, or activated -SH group is associated with a cysteine residue of said target protein | Page 9, line 22; page 10, lines 12-16 |
| 67 | said disulfide bond is formed under reducing conditions | Page 27, lines 17-26 |
| 68 | said disulfide bond is formed in the presence of a reducing agent | Page 27, lines 17-26 |

Turning to the Office Action, prior to the entry of the present Preliminary Amendment, Claims 40-41, 44-53, 56 and 63 were pending in this application, and were rejected on various grounds. The current amendment includes the amendment of claim 40 and the addition of new claims 64-68. All rejections and respectfully traversed, and will be specifically addressed in the arguments below. Since most rejections are essentially repeated from the previous Office Action (Paper No. 11), all arguments made in Applicants' response dated May 19, 2003 are hereby expressly incorporated by reference.

## I.

***Claim Rejections – 35 USC §112, first paragraph***

Claims 40-41, 44-53, 56 and 63 were rejected under 35 USC §112, first paragraph fir alleged lack of written description for the claimed genus. This rejection has essentially been repeated from the previous Office Action. In addressing Applicants' rebuttal arguments, the Examiner noted that "the target protein(s), ligand(s) and linker(s) are critical to the invention because the claimed "tethering" method could not be performed without them. . .If Applicants do not have possession of all the claimed target protein(s), ligand(s) and linker(s) then Applicants do not have possession of all the methods for using said protein(s), ligand(s) and linkers(s)." The Examiner adds that in order to provide adequate written description for the "infinite number of possibilities" claimed, Applicants must provide "a representative number of examples," and, again, refers to the teaching provided in the specification as reciting a "laundry list" of potential ligands, chemically reactive groups and target proteins, which, in the Examiner's view, does not qualify as the specific teaching required by law. In response to Applicants' request to provide specific scientific reasoning for the finding that the claimed genus is not enabled, the Examiner cites DeLano, *Current Opinion in Structural Biology* 2002, 12, 14-20, but notes that "the Examiner does not believe that such a reference is necessary because . . .Applicants' disclosure of only 'one working example' is not 'representative' of such broad scope." In conclusion, the Examiner, citing the CAFC's holding in *Genentech* 108 F.3d at 1366, qualifies the disclosure of the present application as "a starting point, a direction for further research," "which fails to show essential claimed subject matter with particularity (i.e., the small organic compounds)."

Applicants submit that the present rejection is based on a misunderstanding and misapplication of the relevant case law, and vigorously traverse the rejection.

*Applicants' Rebuttal of the Rejection*

As a preliminary matter, the Examiner is incorrect in stating that the citation of the DeLano reference was not necessary, and the reference has been cited only to adhere to Applicants' request to provide specific scientific reasoning why one skilled in the art would not accept that at the effective filing date of the present application applicants were in the possession of the invention. It is not Applicants but the law, and its implementation in the Revised Written Description Guidelines, that mandate the Examiner to provide evidence or specific reasoning why a skilled artisan would doubt Applicants' assertion of written description thereby meeting his burden of proof.

A mere assertion that '"one" example is not sufficient to teach an infinite number of possibilities that are currently claimed" clearly does not meet the Examiner's burden of establishing a *prima facie* case of lack of adequate written description. This is particularly so, since **the law does not require the presence of a representative number of "*examples*" to enable a genus**. Instead, written description for a claimed genus may be satisfied through ***description*** of a representative number of species. Description may come in a variety of forms, including description in the specification, representation in a drawing, etc. An applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 U.S.P.Q.2D (BNA) 1961, 1966 (1997). The law is clear that it is the "*specification*" as a whole, and *not solely the working examples* that need to be examined in order to determine whether the written description provided is sufficient to support the invention as claimed. Indeed, as evidence of possession, an actual reduction to practice (such as a working example) is not always required, and what is conventional or known to one skilled in the are need not be described (Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 19USPQ2d 1111 (Fed. Cir. 1991). This is also supported by

the CAFC's holding in University of California v. Eli Lilly, where the court stated:

> a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the *recitation* of the sequence of nucleotides that make up the DNA. See Fiers, 984 F.2d at 1171, 25 U.S.P.Q.2D (BNA) at 1606. A description of a genus of cDNAs may be achieved by means of a *recitation* of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a *recitation* of structural features common to the members of the genus, which features constitute a substantial portion of the genus. 119 F.3d 155; 43 U.S.P.Q.2d (BNA) 1398 (1997), emphasis added.

*(a) Written description - small organic molecules*

The claims recite that the small organic molecules screened by the screening assay of the present invention (1) are less than 2000 daltons in size, (2) comprise less than 20 carbon atoms, (3) are soluble and stable in aqueous solution, and (4) carry a chemically reactive group which is capable of covalently bonding to a chemically reactive group on a ligand present in target protein-ligand conjugate.

Contrary to the Examiner's statement that "Applicants provide 'NO EXAMPLES' of the small organic molecules," (emphasis original), the specification provides the following detailed teaching in support of this element of the claimed screening method:

> According to page 13, lines 9-29 of the specification
>
> In the particular embodiment which employs a biological target molecule comprising a first reactive functionality, one may directly screen a library of organic molecules that are capable of forming a covalent bond with the first reactive functionality *or may covalently bond a compound to that first reactive functionality which comprises the chemically reactive group of interest. With regard to the latter, the target molecule comprising the first reactive functionality may be reacted with a compound that comprises (1) a second reactive functionality and (2) a chemically reactive group, wherein that compounds becomes covalently bound to the polypeptide of interest. Specifically, the second reactive functionality of the compound reacts with the first reactive functionality of the target of interest*

*to form a covalent bond, thereby providing a modified target of interest. Preferably, the first and second reactive functionalities are thiol groups, preferably activated thiol groups, that react to form a covalent bond. The target of interest is "modified" in that it now has covalently bound thereto through a covalent bond the compound that comprises the chemically reactive group.* Reaction conditions useful for covalently bonding the compound to the target of interest through a covalent bond are known to those skilled in the art and may employ activating groups such as thiopyridine, thionitrobenzoate, and the like. (Emphasis added.)

According to page 14, lines 10-23

> For the most part, the compound that bonds to the target biomolecules of interest through a covalent, preferably disulfide bond will be relatively small, preferably comprising less than about 20, more preferably less than about 10, more preferably less than about 10, most preferably less than about 5 carbon atoms, although compounds with more carbon atoms may also find use herein. Such compounds will also possess a thiol functionality capable of forming a covalent bond with the free thiol group of the biological target molecule and may also possess other heteroatoms at certain sites within the compound. A particularly preferred compound for use in this embodiment of the invention is thioethylamine or a derivative thereof, such as 2-amino ethanethiol, which is capable of forming a disulfide bond with the free thiol group of the biological target molecule as well as providing a chemically reactive amine group for bonding to members of a library of organic molecules.

Examples of chemically reactive groups are provided in the following passage, and include a primary or secondary amine group that can react with aldehydes or ketones present in the library of small organic compounds. Alternatively, an exemplary chemically reactive group is described an aldehyde or ketone to screen a library of small organic compounds that are primary and/or secondary amines.

A much more extensive listing of the organic compounds that find use in the present invention is provided at page 17, lines 5-23, and includes

> aldehydes, ketones, oximes, hydrazones, semicarbazones, carbazides, primary and secondary amines, hydrazides, alcohols, ethers, thiols, thioethers, thioesters, disulfides, carboxylic acids, esters, amides, ureas, carbamates, carbonates, ketals, thioketals, acetals, thioacetals, aryl

halides, aryl sulfonates, alkyl halides, alkyl sulfonates, aromatic compounds, heterocyclic compounds, anilines, alkenes, alkynes, diols, amino alcohols, oxazolidines, oxazolines, thiazolidines, thiazolines, enamines, sulfonamides, epoxides, aziridines, isocyanates, sulfonyl chlorides, diazo compounds, acid chlorides.

Indeed, the specification teaches that

> virtually any small organic molecule that is capable of covalently bonding to a known chemically reactive functionality may find use in the present invention with the proviso that is sufficiently soluble and stable in aqueous solutions to be tested for its ability to bind to the biological target molecule. (Page 17, lines 18-23.)

Examples of various applicable chemistries are provided, for example, in the passage bridging pages 17 and 18.

Applicants, again, submit that the law does not require to provide a representative number of working examples to enable a genus within the scope of the claims. Indeed, the presence of working examples is not required. The legal requirement is to recite a representative number of species within a claimed genus, from which one skilled in the art would reasonably conclude that Applicants were in the possession of the claimed genus at the time the invention was made. The teaching provided in the specification for the small organic compounds screened by the claimed screening methods clearly meets this requirement.

*(b) Written description - target protein comprising a first reactive functionality*

The Examiner is incorrect in stating that the claimed method "requires" mutations in the target protein. The specification is clear in explaining that the biological target molecule, such as a target protein, is

> "chosen ***such that it possesses or modified to possess*** a chemically reactive group, which is capable of forming a covalent bond with members of a library of small organic molecules. For example, many biological target molecules naturally possess chemically reactive groups (for example, amine

groups, thiol groups, aldehyde groups, ketone groups, alcohol groups and a host of other chemically reactive groups; . . . ) to which members of an organic molecule library may interact and covalently bond. In this regard, it is noted that polypeptides often have amino acids with chemically reactive side chains (e.g., cysteine, lysine, arginine, and the like)." Page 9, lines 13-22; emphasis added.

In cases where the target protein naturally contains a chemically reactive group, the Examiner's reliance on DeLano is irrelevant, since there are no mutations, therefore one need not address the issue of potential destabilizing mutations

In cases where chemically reactive groups, such as cysteines in the case of a protein, are introduced into the target molecule, such derivatization occurs prior to contacting the derivatized target molecule (protein) carrying a first reactive functionality, with a compound comprising a second reactive functionality and a chemically reactive group, in a step that is not included in the claims pending. Therefore, such derivatized target protein is merely a starting material for the invention, which can be obtained from any source, and used after it is validated that the derivatization does not significantly interfere with the target protein-small organic molecule interaction.

*(c) Declaration of Warren L. DeLano, Ph.D. under 37 C.F.R. §1.132*

In further support of Applicants' position, enclosed is a Declaration of Dr. Warren L. DeLano, the author of the cited paper. Dr. DeLano is a founder and CEO of DeLano Scientific L.L.C., a private software company, and has a Ph.D. in Biophysics and a Bachelor of Science Degree in Molecular Biophysics and Biochemistry. Dr. DeLano is, therefore, unquestionably a person skilled in the art. In paragraph 6 of his Declaration, Dr. DeLano confirms that

> the claimed invention does not require mutations. If a suitable reactive group is already present, then the inventive method can be used on the wild type protein.

In paragraph 7, Dr. DeLano explains that

> . . . the concept of "hot spots" is moot with respect to the vast

majority of potential targets because the sited of interest are already known (e.g., active sited with respect to enzymes and ligand binding sites with respect to receptors). As described in my publication, hot spots are relevant to protein-protein and protein-peptide interactions. Because these interactions involve large surface areas, it was previously believed that small molecule modulators of these types of interactions may not be possible. The concept of "hot spots" was developed in part by Dr. James Wells (one of the founders of Sunesis Pharmaceuticals, Inc. and a co-inventor of the claimed invention) when he discovered that a surprisingly few residues were responsible for most of the binding interaction. As a result, a hot spot residue is defined as one that when mutated to alanine, gives rise to a distinct drop in the binding constant. In other words, if a hot spot residue in a protein were mutated to alanine, it results in a destabilizing perturbation at the protein interface such that it disrupts its interaction with its protein partner. Because protein-protein interactions appear to be modulated in large part by these hot spot residues, small molecule modulators directed at such residues could be developed to disrupt such interactions for therapeutic benefit.

In paragraph 8, Dr. DeLano adds that even if the identification of such hot spots becomes necessary, despite the difficulties, such "hot spots can be and are identified."

In paragraph 9, Dr. DeLano states that "the consequences of making mutations of hot spot residues are generally different from those of other residues on protein surfaces," and adds that "identifying residues for making mutants for use in the claimed invention is well within the skill of the art."

Finally, in paragraph 10 of the Declaration, Dr. DeLano confirms that "the claimed invention has been useful for identifying ligands on a variety of protein targets, including those involved in protein-protein interactions."

Accordingly, the Declaration by the author of the cited paper establishes that the Examiner's reliance on DeLano does not support the conclusion that one skilled in the art would doubt that applicants were in the possession of the claimed invention at the

effective filing date of the present application.

*(d) Declaration of Gary W. Ashley, Ph.D. under 37 C.F.R. §1.132*

As further evidence that the claimed genus meets the statutory written description requirement, enclosed with the present Amendment and Response is a Declaration under 37 C.F.R. § 1.132 by Gary W. Ashley, Ph.D. Dr. Ashley, who has over twenty-five years of experience in the relevant field, has read the specification of the present application and the claims currently pending.

In section 5 of his Declaration, Dr. Ashley acknowledges that

> "[t]arget proteins, types of ligands and binding chemistries are extensively described throughout the specification. Based on this disclosure, and also in view of my expertise, it is my considered scientific opinion that the claimed screening method is generally applicable for screening and identifying a variety of small molecule ligands for a variety of target proteins, using a variety of chemistries, as described in the specification and as claimed in the above-identified patent application."

From this, Dr. Ashley concludes that "the inventors were in the possession of the claimed invention at the time the application was filed, within the entire scope of the claims pending."

In view of the foregoing arguments and declaratory evidence, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Should the Examiner maintain the present rejection, he is legally obligated to provide evidence or scientific reasoning in support of such conclusion. The Examiner's view that the genus is "enormous" and "highly variant" and is merely a "laundry list" or a mere "wish" or "plan" would certainly not suffice to rebut Declarations by two experts in the field, one of whom specifically contradicts the Examiner's conclusions drawn from a paper authored by him. The Examiner must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned. It is improper

for the Examiner to substitute his own opinion for that of an expert, or to disregard the opinion of an expert.

## II.

## *Claim Rejections - 35 U.S.C. 102*

(1) Claims 40-41. 44-46 were rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Pitner et al. (U.S. Patent No. 5,367,058). This rejection is maintained from the previous Office Action. In addressing Applicants' earlier arguments, the Examiner explains that in Pitner et al. the "target protein" is the antibody, which is reacting with a "modifying group" (the affinity label) to form a "modified target protein" (i.e. the antibody with a free thiol). In the Examiner's reading, the antibody with the free thiol (without an antigen attached to it) qualifies as a "protein-ligand conjugate." According to the rejection, this reading is justified by the claim language, which does not state that a "ligand" binds to the protein to form a protein-"ligand" conjugate, rather refers to a "compound" as binding to the target protein, "which implies that the 'target protein itself' should be regarded as the 'ligand.'"

Without acquiescence to the Examiner's reasoning, the claims have been amended to clearly recite that the target protein-ligand conjugate is formed by the reaction of a target protein and a ligand, which makes it clear that the affinity labeled antibody of Pitner et al. does not qualify as a target protein-ligand conjugate. This is particularly true since the affinity label described by Pitner et al. does not have affinity for interacting with a particular site on the protein, as required by the current amended claim language (claim 40 and newly added claim 66).

In addition, Pitner et al. does not teach screening of a library of small organic compounds. In Pitner et al., the -SH modified antibody reacts with the antigens one by one; a screening assay is not taught.

Finally, Pitner et al. does not teach a method for determining the identity of the small organic compound. Such method is not needed, since the identity of the antigen to which the antibody binds is known.

For a reference to be anticipatory, it must disclose all elements of the claimed invention. Since Pitner et al. does not disclose several key elements of the invention claimed in the rejected claims, the present rejection should be withdrawn.

(2) Claims 40-41, 44-46 and 56 were rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Janda et al., PNAS 91:2532-2536 (1994). This rejection is also maintained from the previous Office Action. In addressing Applicants' earlier arguments, the Examiner explains that, due to the inconsistent use of the terms "ligand" and "compound" in the claims, compound of formula 1 does not have to be a "ligand" in order to fall within the scope of claim 40. The Examiner adds that "'compound 1' is a 'ligand' because it does not need to have an 'affinity for a particular site.'"

Since the current claims consistently refer to a "ligand" eliminating the use of the term "compound" that was found confusing by the Examiner, and further since the current claims recite the requirement that the ligand need to have an affinity for a particular site, the Examiner is respectfully requested to withdraw the present rejection.

**III.**

***Claims Rejections - 35 USC § 103***

(1) Claims 40-41, and 44-49 were rejected as allegedly being obvious over Pitner et al. and Loo et al., *Mass Spectrometry Reviews* 16:1-23 (1997).

Pitner et al. was applied as in the previous rejection under 35 U.S.C. § 102(b). The Examiner notes that since Pitner et al. anticipates claims 40-41 and 44-46, it also renders obvious those claims. Loo was cited for the teaching of mass spectroscopy for

the identification of protein-ligand interactions.

As argued in response to the previous rejection, Pitner et al. does not anticipate claims 40-41 and 44-46. Nor does this primary reference render obvious the rejected claims. The present invention concerning a screening assay by an approach when a library of small organic compounds is screened with a protein-ligand conjugate carrying a reactive group, and the library member(s) that is/are capable of covalently bonding to the conjugate are identified. Pitner et al. has no disclosure or hint of a similar screening assay. Indeed, Pitner et al. concerns antibodies modified by an affinity label in order to increase their affinity for their known ligands. It is easy to see that the disclosure of Pitner et al. provides no motivation for the development of a screening assay like that disclosed and claimed in the present application.

The only applicable teaching of the secondary reference is the teaching of mass spectroscopy to monitor protein-ligand interactions. Accordingly, the secondary reference does not remedy the deficiencies of Pitner et al., and the present rejection should be withdrawn.

(2) Claims 40-41, 44-48 and 56 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Pitner et al. and Ganem et al.

Pitner et al has been discussed above. Ganem et al. has been cited for its disclosure of mass spectroscopy methods for identifying enzyme-substrate and receptor-ligand complexes. As pointed out in Applicants' response to the previous obviousness rejection, Pitner et al. has no teaching, suggestion or hint whatsoever that would motivate one skilled in the art to try to develop a screening assay as that disclosed and claimed in the present application. Furthermore, it has no disclosure, suggestion or hint that would communicate to one skilled in the art that such screening method can be developed with a reasonable expectation of success.

Since Ganem is applied only for its disclosure of mass spectroscopy methods, it does not remedy the deficiencies of Pitner et al. Accordingly, the cited combination of references does not make obvious the claimed invention, and the present rejection should be withdrawn.

(3) Claims 40-41 and 44-52 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Pitner et al. and Przybylski et al. Pitner et al. was applied as in the previous rejections. Przybylski et al. was cited for its reaching of the use of mass spectroscopy for monitoring receptor-ligand interactions, including antibody-antigen interactions, and for identifying a ligand by mass spectroscopy, without purification.

As pointed out in Applicants' response to the previous obviousness rejection, Pitner et al. has no teaching, suggestion or hint whatsoever that would motivate one skilled in the art to try to develop a screening assay as that disclosed and claimed in the present application. Furthermore, it has no disclosure, suggestion or hint that would communicate to one skilled in the art that such screening method can be developed with a reasonable expectation of success.

Przybylski has been relied upon for its teaching of mass spectroscopy detection methods, and has no disclosure that would substitute for the teaching or motivation missing in Pitner et al. In addition, Przybylski et al. discusses the use of electrospray mass spectrometry of biomacromolecular complexes with *noncovalent* interactions. Accordingly, its teaching is not directly applicable to the detection of covalent interactions by mass spectroscopy, as disclosed and claimed in the present application.

In view of the foregoing arguments, the Examiner is respectfully requested to withdraw the present rejection.

(4) Claims 40-41, 44-52, and 56 were rejected under 35 U.S.C. § 103(a) over Janda et al. and Przybylski et al. The two references have been applied as in the previous rejections.

As discussed earlier, contrary to the Examiner's assertion, Janda et al. does not teach all the limitations of claims 40-41, 44-46, and 56, and consequently does not anticipate those claims. Nor does Janda et al. have any disclosure, suggestion or hint that would motivate one skilled in the art to develop the screening assay of the present invention, and do it with a reasonable expectation of success.

Przybylski et al. has been discussed in response to the previous rejection, and does not fill in the gaps left by Janda et al. for essentially the same reasons.

Since the cited combination of references does not make obvious the invention claimed in the rejected claims, the reconsideration and withdrawal of the present rejection is respectfully requested.

(5) Claims 40-41 and 44-53 were rejected under 35 U.S.C. § 102(a) as allegedly being unpatentable over Pitner et al. and Przybylski et al. and Crooke et al. (U.S. Patent No. 6,428,956).

Pitner et al. and Przybylski et al. have been applied as discussed above, and, when taken alone or in combination do not render obvious the claimed invention for reasons set forth in Applicants' response to the previous rejection.

Crooke et al. was cited as relevant to claim 53, for its alleged disclosure of labeled probes. Since Applicants have shown that claim 40 (and by analogy, new independent claim 66) are novel and unobvious over the combination of Pitner et al. and Przybylski et al., all dependent claims, which carry all limitations of the independent claims on which they depend, are novel and unobvious for the same reasons. Accordingly, Applicants are

not legally required to show additional unobvious features for the embodiment claimed in claim 53, and the withdrawal of the present rejection is respectfully requested.

(6) Claims 40-41, 44-53 and 56 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Janda et al. and Przybylski et al. and Crooke et al. The references have been applied as in the previous rejections.

Applicants have shown that the combined teaching of Janda et al. and Przybylski et al. does not make obvious the claimed invention. Since Applicants have shown that claim 40 (and by analogy, new independent claim 66) are novel and unobvious over the combination of Janda et al. and Przybylski et al., all dependent claims, which carry all limitations of the independent claims on which they depend, are novel and unobvious for the same reasons. Accordingly, there is no need for Applicants to show additional unobvious features for the embodiment claimed in claim 53, and the withdrawal of the present rejection is respectfully requested.

(7) Claims 40-41, 44-52 and 63 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Pitner et al. and Przybylski et al. and Wunsch et al. and Tam (U.S. Patent No. 6,310,180). The is a new rejection.

Applicants have already shown that the combined teaching of Pitner et al. and Przybylski et al. does not anticipate or render obvious claims 40-41 and 44-52. Wunsch et al. and Tam et al. were cited with regard to claim 63 only. Since claims 40-41 and 44-52 are novel and unobvious over the cited combination of primary references, claim 63 is novel and unobvious for the same reasons. Accordingly, it is irrelevant whether the specific embodiment claimed in claim 63 shows any additional unobvious features over the cited combination of four references, and the present rejection should be withdrawn.

## IV.

### *Claims Rejections - 35 U.S.C. 112, second paragraph*

Claim 40 was rejected since, in the Examiner's view, the phrase "ligand in the protein-ligand conjugate" is vague as a result of Applicants' inconsistent use of the terms "ligand" and "compound." Claim 40 was further rejected, since the term "ligand" in the 7th line was found to have no antecedent basis. Since the claim now consistently refers to a "ligand," these rejections are believed to be moot.

Claim 48 was further rejected for its reference to a "target protein-ligand conjugate" since the term was found to have insufficient antecedent basis in the claim. Claim 48 depends on claim 47 which in turn depends on claim 40. Since claim 40 not recites a target protein-ligand conjugate, the present rejection is moot.

## V.

### *Claim Rejections - 35 U.S.C. 112, first paragraph*

Claims 40-41, 44-53, 56 and 63 were rejected for allegedly containing new matter. According to the rejection, the phrase "target molecule" present in claim 40 extends to go beyond the definition of "biological target molecule" and is, therefore, new matter. Without acquiescing to the rejection, the term objected to is no longer present in clam 40, therefore, the present rejection should be withdrawn.

## VI.

### *Double Patenting*

Claims 40-41, 44-53, 56 and 63 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-39 of

U.S. Patent Publication 2002/0022233 A1 and U.S. Patent Application Publication 2002/0081621. In response to Applicants' earlier argument that the rejection, which was believed to be the only remaining rejection, should be withdrawn and, if appropriate, repeated in the other pending application, the Examiner argued that an appropriate terminal disclaimed must be filed "in each application."

The Examiner's attention is respectfully directed to M.P.E.P. 804 I.B. which, in its relevant part, states:

> The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications. **If the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent**, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issue as a patent. (Emphasis added.)

Accordingly, the procedure advocated by Applicants in the correct procedure set forth in the M.P.E.P. Nonetheless, solely to expedite prosecution, Applicants have enclosed a terminal disclaimer, which should overcome the present rejection.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early issuance of a Notice of Allowance is respectfully solicited.

The Commissioner is hereby authorized to charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39750-0002DV1C1). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: October 27, 2003

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